Effective Dose of Sedation in Transesophageal Echocardiography – Relation to Age, Body Surface Area and Left Ventricle Function

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Abstract

Background: Sedation with midazolam and meperidine is widely used in transesophageal echocardiography. However, no mean dose is established for each individual case.

Objective: To correlate the mean midazolam and meperidine doses for proper sedation for transesophageal echocardiography with age range, body surface area, and left ventricular ejection fraction.

Methods: Retrospective study comprising 1,841 patients undergoing sedation based on the Ramsay scale, with a solution containing midazolam 1.5 mg (1.5 ml), meperidine 1 mg (1 ml) and distilled water (7.5 ml). Four age groups were analyzed: G1: ≤ 24 years; G2: 25 to 44 years; G3: 45 to 64 years; and G4: ≥ 65 years. Body surface area was calculated using the formula {[(height x 100)$^{0.725}$] x (weight$^{0.425}$) x 0.0071}. As regards the left ventricular ejection fraction, two groups were studied: GA: < 55%; and GB: ≥ 55%. The statistical analysis was carried out using the Kruskal-Wallis test for the correlation with age and left ventricular ejection fraction, and simple linear correlation for body surface area.

Results: As regards age, the mean doses of sedation required were significantly lower in G3 and G4 ($p<0.01$). The analysis of left ventricular ejection fraction showed that this was significantly lower in GA ($p<0.01$). The linear correlation coefficient between dose of sedation and body surface area was 0.09 (null).

Conclusion: The mean dose of sedatives required was lower in older individuals and in those with left ventricular systolic dysfunction. No correlation with body surface area was found. (Arq Bras Cardiol 2009; 93(6):576-581)

Key Words: Midazolam; transesophageal echocardiography; meperidine; conscious sedation.

Introduction

Transesophageal echocardiography is performed via esophageal intubation, using a probe with one or more transducers at its tip. An approximately 5-hour fast is required for all patients undergoing the procedure whether using anesthesia or sedation[1].

The use of a local anesthetic agent (lidocaine hydrochloride 10% spray) and peripheral venipuncture are also recommended; usually, sedatives and analgesic agents are preferably administered intravenously[1]. The tolerance to the procedure, which is almost always uncomfortable, is increased with the use of sedation and analgesia by blocking the response to stress (quite useful in patients with heart diseases), and by reducing the laryngeal activity (very useful in patients with asthma, chronic bronchitis and heart diseases), discomfort and pain. It is also very useful for excessively anxious patients and those with neurological diseases or psychiatric disorders who are unable to cooperate. It can also be performed as per patient request[2]. Today, the drugs most frequently used for sedation in transesophageal echocardiography are the benzodiazepines (diazepam and midazolam), and for analgesia, the opioids (meperidine and fentanyl) and propofol. Adequate levels of sedation based on the use of low doses of sedatives are preferred because of the higher tolerability to the procedure and minimum incidence of side effects[3-6].

Because of the importance of standardizing the amount of sedatives and analgesic drugs necessary for an adequate sedation in groups of patients with specific characteristics[7], we studied the correlation between the mean doses of midazolam and meperidine solution required to achieve a level of sedation between 3 and 4 of the Ramsay scale (Table 1) in individuals from different age ranges, in those with different body surface areas, and in patients diagnosed with or without left ventricular systolic dysfunction.

Methods

A total of 1,841 patients undergoing transesophageal echocardiography for different clinical indications in our institution were retrospectively analyzed. They were aged between 14 and 96 years (mean of 53.5 ± 16.9 years), and 944 (51.3%) of them were males.

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Table 1 - Ramsay scale for the assessment of the level of sedation

LEVEL OF ACTIVITY	POINTS
Patient anxious, agitated or restless	1
Patient cooperative, orientated and tranquil	2
Patient responding only to verbal commands	3
Patient with brisk response to light glabella tap or loud auditory stimulus	4
Patient with sluggish response to light glabella tap or loud auditory stimulus	5
Patient with no response to light glabella tap or loud auditory stimulus	6

The tests were performed according to the Standardization of Equipment and Examination Techniques for Echocardiographic Studies of the Brazilian Society of Cardiology[1].

In all patients, transthoracic echocardiography was performed, and immediately followed by transesophageal echocardiography[8]. General Electric ultrasound scanners, model Vivid 3 equipped with 2.5 MHz transthoracic transducers and 5-MHz transesophageal transducers were used.

The transthoracic and transesophageal studies were performed in an outpatient setting, in a room equipped with instruments and medications for cardiopulmonary resuscitation.

Left ventricular ejection fraction was measured by the transthoracic technique. Simpson's rule was used in patients with segmental wall motion abnormalities; in the remaining patients, the cube or the Teichholz methods were used when the left ventricular end diastolic diameter was equal to or lower than 60 mm, or higher than 60 mm, respectively[9,10]. The cut-off point adopted for left ventricular systolic dysfunction was the ejection fraction of 55%, because ejection fractions lower than this value characterize the presence of ventricular systolic dysfunction regardless of the method used.

Patients were monitored during the transesophageal study with a pulse oximeter for the observation of peripheral oxygen saturation; with a cardiac monitor for observation of the continuous electrocardiographic tracing and heart rate; and with non-invasive blood pressure measurement by means of a stethoscope and a mercury-column sphygmomanometer immediately before the procedure, after the expected level of sedation was achieved, and immediately after the end of the procedure.

Topical anesthesia of the mouth, oropharynx and hypopharynx was made with lidocaine hydrochloride 10% spray, in order to facilitate the introduction of the transducer. The maximum dose used was 4mg/kg, so as to prevent occasional toxicity[11-13]. Sedation was made with a standard 10ml solution containing 1.5 mg of the benzodiazepine midazolam, corresponding to 1.5 ml of the solution, and 1 mg of the opioid analgesic drug meperidine, corresponding to 1 ml of the solution, diluted in 7.5 ml of distilled water, thus resulting in 0.15 mg of midazolam combined with 0.1 mg of meperidine per mL of solution.

The Ramsay scale was used for the analysis of the patients' level of sedation, and effective sedation was standardized as the response to verbal stimulus alone or accompanied by tactile or auditory stimulus, corresponding to the scores 3 and 4 of the scale[14] (Table 1).

The desired level of sedation was achieved for each patient using intravenous bolus injection of 1 ml of midazolam and meperidine solution, with up-titration by 1 ml every minute, if necessary, until the level of sedation as established by the Ramsay scale was achieved.

After the procedure, all patients were transferred to the post-anesthesia recovery room, where their vital signs were monitored by a cardiac monitor and pulse oximeter throughout their stay. Also, non-invasive blood pressure was measured with a stethoscope and mercury-column sphygmomanometer immediately prior to discharge.

Pharmacologic reversal of sedation was required in 2.12% of the patients, corresponding to 39 individuals, due to the occurrence of a level of sedation above 4 points in the Ramsay scale in 26 patients; hypoxemia in five patients; systemic hypotension in four patients; and apnea in three patients. The benzodiazepine antagonist flumazenil and the opioid antagonist naloxone were used in all cases, in addition to respiratory support and fluid replacement in the cases of hypotension. Initially, boluses of 0.2 mg flumazenil and 1mg naloxone for 15 seconds were administered. If necessary, additional 0.1mg flumazenil and 1mg naloxone doses were given for 15 seconds every 3 minutes, until the adverse effects produced by midazolam and meperidine were reverted. A maximum dose of 1mg for flumazenil and 10mg for naloxone was established.

Patients were discharged when an adequate level of conscience had been reestablished, corresponding to scores 1 and 2 of the Ramsay scale (Table 1). All were discharged after adequate medical evaluation and were asymptomatic and with blood pressure, heart rate, peripheral oxygen saturation and electrocardiographic tracing within normal limits for adult patients at rest. In order to study the correlation between the effective sedative dose and the age variable, the patients were divided into four different age groups: Group 1 (G1), of individuals aged 24 years or younger (n = 100); Group 2 (G2), between 25 and 44 years of age (n = 457); Group 3 (G3), between 45 and 64 years of age (n = 721); and Group 4 (G4), aged 65 years or older (n = 563). The expected level of sedation was achieved for the patients of each group; then, the mean amount of solution required for each group was established. Because of the heterogeneity of the study population, the non-parametric Kruskal-Wallis test was used for the comparison between groups.

Body surface area (BSA) was calculated for each patient using the formula BSA = $\{[(\text{height} \times 100)^{0.725}] \times (\text{weight}^{0.425}) \times 0.0071\}$. Simple linear regression with numerical analysis of data in the scatter plot was used for the correlation between the independent variable (body surface area) and the dependent variable (effective dose of the midazolam and meperidine solution). The scatter plot comprised a set

of dots formed by the intersection of x-axis values (body surface area) and y-axis values (dose of midazolam and meperidine solution required to achieve the expected level of sedation) for each patient. The conclusion on whether the correlation between these two variables was positive, negative or null was established using the linear correlation coefficient (r).

In order to study the correlation between the effective dose of sedative and the left ventricular systolic function variable, the patients were divided into two groups: Group A (GA), with ejection fraction lower than 55% (n=222); and Group B (GB), with ejection fraction equal to or higher than 55% (n=1,619). Like for the study of the age variable, the expected level of sedation was obtained for the patients of each group; then, the mean amount of solution necessary for each group was established. The non-parametric Kruskal-Wallis test was used for the comparison between the two heterogeneous groups of patients.

Prior to undergoing the tests, all patients gave their written informed consent to participate in studies to be conducted in the institution.

Retrospective data were obtained from the electronic echocardiographic reports of the patients studied. The study protocol was approved by the institutional research ethics committee according to the ethical recommendations of the Declaration of Helsinki, 1975.

Results

Study population

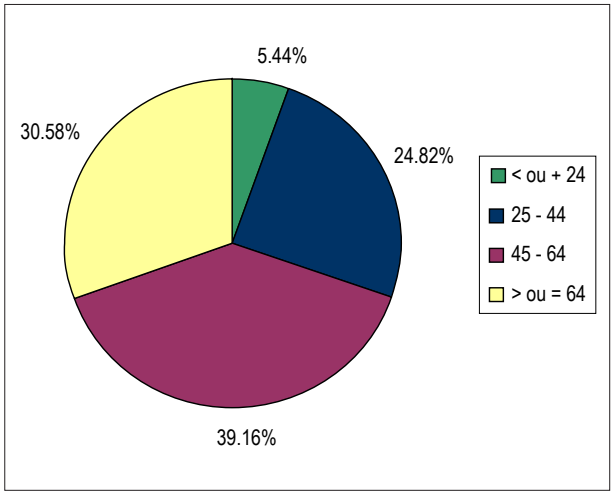
The present study was characterized by having a balanced proportion between male individuals (51.3%), in a total of 944 patients, and female individuals (48.7%), representing 897 patients. As regards the age ranges studied, the number of individuals increased in the groups up to the age of 64 years, to further show a slight decrease, as observed in Graph 1.

Mean effective doses of midazolam and meperidine solution related to the different age groups

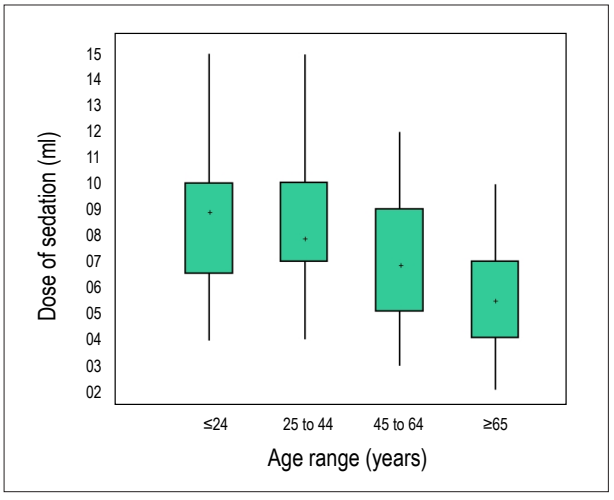
For the analysis of the four age groups included in the study, the mean doses of midazolam and meperidine solution required to achieve sedation between levels 3 and 4 of the Ramsey scale were established for each group and compared between themselves. The result, as demonstrated in Graph 2 and Table 2, showed that the mean dose of sedative solution required was inversely proportional to the increase in age, thus higher in Group 1, which was comprised of the youngest individuals. From Group 2, and progressively up to Group 4, a significant reduction in the mean doses of solution ($p<0.01$) was observed, more markedly among the oldest patients, that is, those belonging to Group 4, ageing 65 years and older. Using Group 1 as a reference, the percentage reduction of the mean effective doses of sedative solution in the other groups was as follows: Group 2 (1.90%), Group 3 (19.78%) and Group 4 (36.65%).

Mean effective doses of midazolam and meperidine solution related to body surface area

The analysis of each patient's body surface area, as calculated using the formula BSA = $\{[(\text{height} \times 100)^{0.725}] \times (\text{weight}^{0.425}) \times 0.0071\}$, showed values ranging from a minimum of 1.22m^2 to a maximum of 2.67 m^2 for all the 1,841 individuals studied, thus establishing an overall mean of approximately 1.79 ± 0.21 m^2. Using the simple linear regression as a statistical tool, we established the value of linear correlation coefficient (r=0.09) between the independent variable (body surface area) and the dependent variable (dose of midazolam and meperidine solution required for sedation between levels 3 and 4 of the Ramsay scale) by means of the data interpreted from the analysis of the scatter plot (Graph 3). The interpretation of this coefficient resulted in a null linear correlation between the two variables.



Graph 1 - Percentage of individuals by age range (years).

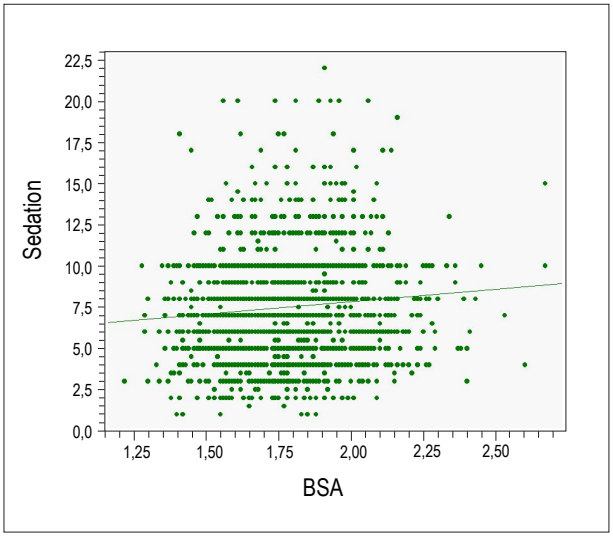


Graph 2 - Mean dose of midazolam and meperidine solution by age range

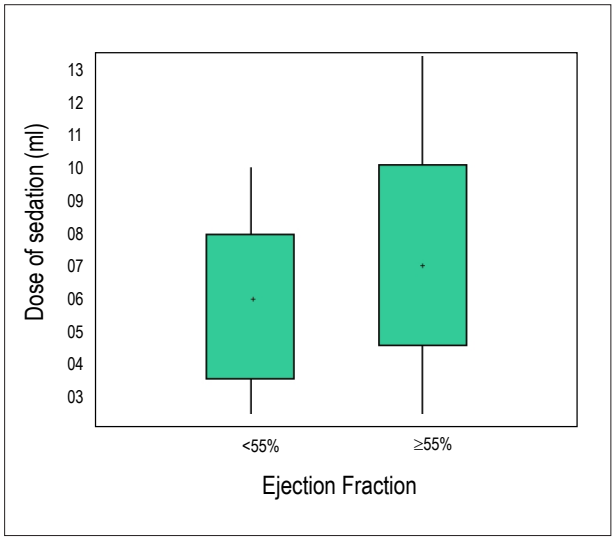
Table 2 - Mean dose of midazolam and meperidine solution by age range

	Midazolam and meperidine solution		
Age ranges (years)	Mean dose of solution (ml)	Mean dose of midazolam (mg)	Mean dose of meperidine (mg)
G1 (≤ 24 years)	8.95	1.34	0.89
G2 (25 to 44 years)	8.78	1.31	0.87
G3 (45 to 64 years)	7.18	1.07	0.71
G4 (≥65 years)	5.67	0.85	0.56
Total	30.58	4.57	3.03

G1 - group 1; G2 - group 2; G3 - group 3; G4 - group 4



Graph 3 – *Correlation between mean dose of midazolam and meperidine solution and body surface area (BSA)*



Graph 4 – *Dose of Midazolam and meperidine solution by left ventricular ejection fraction range*

Mean effective doses of midazolam and meperidine solution related to the left ventricular systolic function

There was a direct proportion between the doses of midazolam and meperidine solution and left ventricular ejection fraction, as demonstrated in Graph 4 and Table 3. Group A, with the lowest ejection fraction, required a significantly lower mean dose (6.29 ± 2.70 ml), in comparison with Group B (7.34 ± 3.15 ml), to achieve the expected sedative effect ($p < 0.01$). The percentage of reduction in the mean dose of sedative solution from Group 1 to Group 2 was 14.3%.

Discussion

The objective of this study was to determine the correlation between the mean doses of midazolam and meperidine solution required to achieve a level of sedation corresponding to scores 3 and 4 of the Ramsay scale in patients undergoing transesophageal echocardiography, and three independent variables: age range, body surface area, and left ventricular ejection fraction.

The Ramsay scale was used to analyze the level of sedation because it has been widely applied by several authors and in studies related to anesthesiology and intensive care, and also for its acknowledged quality in the assessment of the level of sedation[15].

Midazolam, a short-acting drug derived from the group of the imidazobenzodiazepines, is used intravenously in transesophageal echocardiography for anxiolytic, sedative, hypnotic and amnestic purposes[16]. It strongly binds to plasma proteins (95 ± 2%), has a high volume of distribution (1.1 ± 0.6 liters/kg), high systemic clearance (6.6 ± 0.8 ml/min. kg), and a low elimination half-life (1.9 ± 0.6 hours). Its biotransformation occurs in the liver via hydroxylation of the methyl group on the imidazole ring. Its most active metabolite is 1-hydroxymethylmidazolam, whose elimination half-life is one hour after conjugation with the glucuronic acid. The main route of excretion is the kidney (56 ± 26%)[17].

Meperidine, in turn, is a short-acting opioid from the group of the phenylpiperidines, used intravenously in transesophageal echocardiography because of its potent analgesic action. It moderately binds to plasma proteins (58 ±

Table 3 - Mean dose of midazolam and meperidine solution by left ventricular ejection fraction range

	Midazolam and meperidine solution		
Left ventricular ejection fraction (LVEF) %	Mean dose (ml)	Midazolam (mg)	Meperidine (mg)
GA (LVEF < 55%)	6.29	0.94	0.62
GB (LVEF ≥ 55%)	7.34	1.10	0.73
Total	13.63	2.04	1.35

GA – group A; GB – group B

9%), has a high volume of distribution (4.4 ± 0.9 liters/kg), high systemic clearance (17 ± 5 ml/min.kg) and a low elimination half-life (3.2 ± 0.8 hours). Its biotransformation occurs in the liver by oxidation and reduction reactions via the cytochrome P450/hydrolysis and conjugation. The main route of excretion is the kidney (approximately 25% at low urine pH), but the biliary and gastrointestinal routes are also a possibility[18,19].

Overall, as a consequence of the aging process, the hepatic changes resulting from a reduction in organ mass, enzyme activity, and blood flow to the hepatocytes determine the drop in its global metabolic activity. Reduced capacity of biotransformation of drugs with a high percentage of liver participation, such as midazolam and meperidine, is expected in the elderly, and this leads to a prolonged plasma half-life and increased serum levels of their metabolically active molecules[20-22].

Patients with left ventricular ejection fraction lower than normal present with multiple morphological and functional liver changes caused by the reduced blood flow to the hepatocytes, ranging from mild abnormalities in functional tests to progressive fibrosis with cardiac cirrhosis and cardiogenic ischemic hepatitis. These changes are closely related to the alterations in the pharmacokinetics of the drugs metabolized by the liver, as is the case of midazolam and meperidine, and are reflected in the prolonged plasma half-life and increased serum levels of their metabolically active molecules, as a result of the deceleration of their systemic clearance[23]. In relation to midazolam and meperidine, in patients with left ventricular systolic dysfunction, this deceleration results from a reduction in the hydroxylation processes in the case of midazolam, and in the metabolic activity of the cytochrome P450 monooxygenase in the case of meperidine.

The prolonged plasma half-life and increased serum levels of their metabolically active compounds result in prolonged and more intense pharmacological effects, and lower doses of the drugs used in the elderly and patients with left ventricular systolic dysfunction are frequently necessary. Thus, the purpose is to achieve the desired clinical effects with less toxic effects[20].

The study of the age range and left ventricular systolic function variables showed a close concordance with data from the literature[20-23]. The analysis of age range showed that the mean doses of midazolam and meperidine solution required to achieve the expected level of sedation were progressively lower the higher the age range of the patients studied; the maximum percentage of 36.65% reduction of the amount of sedative solution required was achieved in individuals older than 65 years in relation to those younger than 24 years ($p<0.01$). The analysis of left ventricular systolic function showed that the mean dose of sedative solution required was 14.30% lower in patients with systolic dysfunction (ejection fraction lower than 55%) in comparison to those with normal systolic function (ejection fraction equal to or higher than 55%) ($p < 0.01$).

Body surface area is defined as the directly proportional relation between the individual's weight and height, where the weight is characterized by the sum of the fat mass or fat weight, represented by all lipids in the organism, and the lean mass, represented by water, proteins and mineral components[24]. In individuals with high body surface areas characterized as obese, that is, individuals with a total body weight disproportionately high in relation to height, midazolam pharmacokinetics is modified by its increased volume of redistribution, with subsequent increase in its plasma half-life, thus causing more prolonged pharmacological effects in comparison to non-obese individuals[25]. The primary distribution of intravenously administered midazolam in the central nervous system and other organs with high blood supply is not affected by obesity. This distribution occurs a few seconds after drug administration, followed by a redistribution phase to organs with lower blood supply, especially the muscle and adipose tissues, and this is the pharmacokinetic phase that is influenced by obesity, when the primary effects of midazolam on the central nervous system, such as sedation, hypnosis, and antegrade amnesia, are already established[17]. The pharmacokinetic characteristics of meperidine, in turn, are similar in obese and non-obese individuals[19].

It is intuitive to imagine that individuals with higher body surface areas require higher amounts of sedatives. However, in our study, no correlation was found between the doses of midazolam and meperidine solution required and the patients' body surface areas. The null correlation coefficient between these two variables is consistent with data from the literature[16,19,25]. Therefore, no proportionality between the doses of sedative solution required and the different body surface areas is observed. This demonstrates that individuals with large body surface areas may require lower doses of sedative solution, in the same fashion that those with small areas may require higher doses of the solution.

As a study limitation, we can mention the fact that other factors that could interfere with the hepatic metabolism of midazolam and meperidine, such as alcohol use, concomitant liver diseases, and competition for the same biotransformation route with other drugs, were not analyzed. Also, since this was a retrospective study, left ventricular ejection fraction was obtained from the patients' electronic medical records using three different methods (cube, Simpson and Teichholz). However, we believe this did not affect the study results, since the cut-off value of 55% tells apart individuals with or without left ventricular dysfunction, regardless of the method used.

Conclusion

Our findings indicate that the mean midazolam and meperidine solution doses required to obtain sedation between levels 3 and 4 of the Ramsay scale in transesophageal echocardiography are significantly lower the higher the patient's age and the lower their ejection fraction. Also, no correlation was found between the dose of sedation and body surface area of the patients studied.

These results provide the possibility of obtaining a more precise reference on the amount of midazolam and meperidine required for an adequate level of sedation during transesophageal echocardiography in these specific patient groups.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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